## REMARKS

Status of the Claims

Claims 1-50 and 60 were withdrawn from further consideration in response to a restriction requirement by the Examiner, under 37 C.F.R. §1.142(b). Thus, claims 51-59 and 61-69 are presented for reconsideration.

*Pending claims*

Claims 29 to 54, added in the preliminary amendment dated February 24, 2000, are pending (claims 1 to 28 were canceled).

*Restriction Requirement and Election*

In the restriction requirement dated January 11, 2002, the Patent Office alleged that the pending claims of the application were directed to twenty separate and distinct inventions under 35 U.S.C. §121:

Group I: Claims 1-9, and 16-44, drawn to a chimeric polypeptide molecule comprising RGD motif polypeptide comprises SEQ ID NO: 1 and pharmaceutical formulation thereof, classified in Class 530, subclass 350; class 514, subclass 2.

Group II: Claims 1-4, 10, 11, and 16-44, drawn to a chimeric polypeptide molecule comprising E-selectin binding polypeptide comprises SEQ ID NO: 2 and pharmaceutical formulation thereof; classified in Class 530, subclass 350; class 514, subclass 2.

Group III: Claims 1-4, 12, 13, and 16-44, drawn to a chimeric polypeptide molecule comprising MMP comprises SEQ ID NO:3 polypeptide and pharmaceutical formulation thereof, classified in Class 530, subclass 350; class 514, subclass 2.

Group IV: Claims 1-4, and 14-44, drawn to a chimeric polypeptide molecule comprising proteoglycan binding polypeptide comprises SEQ ID NO: 4 and pharmaceutical formulation thereof, classified in Class 530, subclass 350; class 514, subclass 2.

Group V: Claims 1-4, and 15-44, drawn to a chimeric polypeptide molecule comprising proteoglycan binding polypeptide comprises SEQ ID NO: 5 and pharmaceutical formulation thereof, classified in Class 530, subclass 350; class 514, subclass 2.

Group VI: Claims 45-50, drawn to a nucleic acid encoding chimeric RGD polypeptide comprises SEQ ID NO: 1, vector and host cells and pharmaceutical formulation thereof, classified in Class 536, subclass 23.4; Class 435, subclasses 69.1, 252.3, and 320.1.

Group VII: Claims 45-50, drawn to a nucleic acid encoding chimeric E-selectin polypeptide comprises SEQ ID NO: 2, vector and host cells, classified in Class 536, subclass 23.4; Class 435, subclasses 69.1, 252.3, and 320.1.

Group VIII: Claims 45-50, drawn to a nucleic acid encoding chimeric MMP polypeptide comprises SEQ ID NO: 3, vector and host cells, classified in Class 536, subclass 23.4; Class 435, subclasses 69.1, 252.3, and 320.1.

Group IX: Claims 45-50, drawn to a nucleic acid encoding chimeric chondroitin sulfate proteoglycan polypeptide comprises SEQ ID NO: 4, vector and host cells, classified in Class 536, subclass 23.4; Class 435, subclasses 69.1, 252.3, and 320.1.

Group X: Claims 45-50, drawn to a nucleic acid encoding chimeric chondroitin sulfate proteoglycan polypeptide comprises SEQ ID NO: 5, vector and host cells, classified in Class 536, subclass 23.4; Class 435, subclasses 69.1, 252.3, and 320.1.

Group XI: Claims 51-59, drawn to methods of *in situ* and *in vivo* imaging comprising RGD polypeptide comprises SEQ ID NO: 1 chimeric molecule, class 424, subclass 138.1 and 146.1.

Group XII: Claims 51-59, drawn to methods of *in situ* and *in vivo* imaging comprising E-selectin binding polypeptide comprises SEQ ID NO: 2 chimeric molecule, class 424, subclass 138.1 and 146.1.

Group XIII: Claims 51-59, drawn to methods of *in situ* and *in vivo* imaging comprising MMP comprises SEQ ID NO: 3 chimeric molecule, class 424, subclass 138.1 and 146.1.

Group XIV: Claims 51-59, drawn to methods of *in situ* and *in vivo* imaging comprising chondroitin sulfate proteoglycan binding polypeptide comprises SEQ ID NO: 4 chimeric molecule, class 424, subclass 138.1 and 146.1.

Group XV: Claims 51-59, drawn to methods of in situ and in vivo imaging comprising chondroitin sulfate proteoglycan binding polypeptide comprises SEQ ID NO: 5 chimeric molecule, class 424, subclass 138.1 and 146.1.

Group XVI: Claim 60, drawn to a method of screening comprising RGD binding polypeptide comprises SEQ ID NO: 1 chimeric molecule; classified in Class 435, subclass 7.1.

Group XVII: Claim 60, drawn to a method of screening comprising E-selectin binding polypeptide comprises SEQ ID NO: 2 chimeric molecule; classified in Class 435, subclass 7.1.

Group XVIII: Claim 60, drawn to a method of screening comprising MMP binding polypeptide comprises SEQ ID NO: 3 chimeric molecule; classified in Class 435, subclass 7.1.

Group XIX: Claim 60, drawn to a method of screening comprising chondroitin sulfate proteoglycan binding polypeptide comprises SEQ ID NO: 4 chimeric molecule; classified in Class 435, subclass 7.1.

Group XX: Claim 60, drawn to a method of screening comprising chondroitin sulfate proteoglycan binding polypeptide comprises SEQ ID NO: 5 chimeric molecule; classified in Class 435, subclass 7.1.

In response to the Restriction Requirement, Applicants elected Group XI, claims 51-59, drawn to methods of *in situ* and *in vivo* imaging comprising an RGD polypeptide comprising SEQ ID NO:1 chimeric molecule, class 424, subclass 138.1 and 146.1, with traverse. Applicants respectfully noted that claims 51-59, drawn to methods of *in situ* and *in vivo* imaging comprising an RGD polypeptide, are not limited to compositions comprising the exemplary SEQ ID NO:1.

*Right to petition restriction requirement preserved*

In their response of May 13, 2002, Applicants traversed the restriction requirement and respectfully requested the restriction be withdrawn. Applicants set forth distinct and specific errors in the restriction requirement and reasons for the Patent Office to reconsider and withdraw, in part, the restriction requirement. Accordingly, Applicants have preserved their right to petition the restriction to the Group Director under 37 CFR §1.144; see also MPEP §818.03(c); pg 800-60, 8th Edition, August 2001. Applicants will defer submission of the petition (which can be deferred until allowance of the claims).

*Species Requirement and Election*

The Patent Office further alleged that the claims are directed to patentably distinct species. Applicants elected Group XI, claims 51-59, drawn to methods of *in situ* and *in vivo* imaging comprising an RGD polypeptide comprising a chimeric molecule. In the event Applicants elected either of Groups I, II, III or IV, a species election was required for: A) fluorescent B) bioluminescent C) radioactive isotope D) paramagnetic E) chemiluminescent F) heterologous kinase.

Applicants requested reconsideration of the restriction requirement and rejoining of Group I and/or Group VIII with Group XI. Upon rejoining of Group I to Group XI, Applicants elect species E) chemiluminescent, e.g., luciferase.

When the elected species are held to be allowable, Applicants are entitled to consideration (examination) of additional species; if all species are held to be allowable, a generic claim should be allowed (MPEP §809.02(c); pg 800-50, 8th Edition, August 2001).

*Claims added in the instant amendment*

Claims 70 to 75 are added. Thus, after entry of the instant amendment, claims 51 to 59 and 61 to 75 will be pending and under consideration.

*Outstanding Rejections*

Pursuant to the Office Action, claims 51-59 and 61-69 are rejected under 35 U.S.C. §112, first paragraph. Claims 51-59 and 61-69 are rejected under 35 U.S.C. §103 for allegedly being obvious over U.S. Patent No. 5,650,135, in view of U.S. Patent No. 6,087,476, and further in view of U.S. Patent No. 6,180,084. Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

Objections to the Drawings

Applicants herewith submit acceptable corrected Figure 1 and Figure 2 in compliance with 37 CFR §§1.84 and 1.85, as indicated on PTO Form 948.

Issues under 35 U.S.C. §112, first paragraph

*Enablement*

Claims 51-59 and 61-69 are rejected under 35 U.S.C. §112, first paragraph, because it is alleged that the specification, while being enabling for a method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration of a pharmaceutical formulation which comprises a composition comprising a chimeric molecule wherein the chimeric molecule comprises bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 and the image is generated by computer assisted bioluminescent imaging (BLI), does not reasonably provide enablement for imaging of any cell, any tissue, any organ, or a full body as recited in claims 51, 52, 57, 59, and 61-66.[1]

The Patent Office acknowledged that a chimeric molecule comprising a bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 was enabled. However, it was alleged that the specification fails to provide any guidance as to how to make and how to use any "chimeric molecule" for *in situ* or *in vivo* imaging of a cell, a tissue, an organ, or a fully body.[2]

Applicants respectfully aver that the specification enabled the skilled artisan at the time of the invention to make and use the claimed chimeric molecules. The chimeric molecules of the invention have a first domain of a fluorescent, bioluminescent, or chemiluminescent polypeptide, or a heterologous kinase, and a second domain comprising a member selected from an RGD motif-comprising polypeptide, a selectin-binding polypeptide, a matrix metalloproteinase-binding polypeptide, and a chondroitin sulfate proteoglycan-binding polypeptide. The specification provides examples of each of the components of the claimed chimeric molecule.

Fluorescent, bioluminescent and chemiluminescent polypeptides and heterologous kinases were well known in the art at the time of the invention. RGD motifs and RGD-comprising polypeptides were also well known in the art at the time of the invention. Thus, it would have been within the knowledge and skill of the skilled artisan to choose a fluorescent, bioluminescent, or chemiluminescent polypeptide, or a heterologous kinase, and link

[1] See page 3, lines 6-28, of the Office Action.
[2] See page 3, lines 31-35, of the Office Action.

it to a second domain comprising a member selected from an RGD motif-comprising polypeptide, a selectin-binding polypeptide, a matrix metalloproteinase-binding polypeptide, or a chondroitin sulfate proteoglycan-binding polypeptide, to make and use the claimed invention. At the time of the invention, it was well known that RGD motifs are often bound by molecules expressed on tumor cells. At the time of the invention, it was well known in the art that tumor cell-expressing polypeptides that recognize RGD-comprising polypeptides mediate tumor cell adhesion to the components of extracellular matrix and basement membrane.

The Patent Office acknowledged that the specification enables a method for *in situ* or *in vivo* imaging of a tumor neovasculature in an individual comprising administration of a pharmaceutical formulation comprising a chimeric molecule comprising a bioluminescent polypeptide and an RGD motif-comprising polypeptide of SEQ ID NO:1, wherein the image is generated by computer assisted bioluminescent imaging.[3]

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); see also MPEP 2164.01(b), "How to Make the Claimed Invention." If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana*, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993); In MPEP 2164.01(c), "How to Use the Claimed Invention." The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims. See MPEP 2164.02 "Working Example."

The instant specification, including the *in vitro* and *in vivo* working examples, provided sufficient guidance for one skilled in the art to practice the full scope of the claimed

[3] See page 3, lines 7-11, of the Office Action.

invention. For example, Example 1 of the specification demonstrates that the compositions and methods of the invention can be used as a molecular imaging approach to non-invasively detect neovascularization within tumors using *in vivo* models using both a cell culture model and an art-accepted whole animal model (the nude mouse). An exemplary chimeric recombinant polypeptide of the invention, an RGD-containing-luciferase fusion protein, was added to human carcinoma cells in culture. The chimeric RGD-luciferase protein attached to the surface of the cells and could be detected using bioluminescent imaging (BLI). The exemplary RDG-luciferase was also injected into an art-accepted animal model, a nude mouse with an orthotopic mammary tumor. Luciferin was administered. The animal was imaged in an *in vivo* bioluminescent imaging system. As shown in Figure 2, the presence of the tumor was detected by the emission of luciferase-produced photons from the tumor site.

Accordingly, the specification provides a specific example of making and using an exemplary chimeric molecule of the invention (a bioluminescent polypeptide with an RGD motif) to detect *in vivo* an RGD-binding polypeptide by computer assisted bioluminescent imaging. This example with the specification in general also provides the skilled artisan at the time of the invention sufficient guidance to make and use RGD motif-comprising chimeric molecules to detect RGD-binding polypeptides *in vivo* by computer assisted tomography (CAT) image, magnetic resonance spectroscopy (MRS) image, magnetic resonance imaging (MRI) image, positron emission tomography (PET) image, a single-photon emission computed tomography (SPECT) image in addition to bioluminescence image (BLI).

The Patent Office also alleged that while any RGD motif-comprising polypeptide may have some notion of "integrin recognition," claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents commensurate in scope with the claimed invention, and, that minor structural differences among structurally related compounds or compositions can result in insubstantially different biological activities.[4] The Patent Office alleged that sufficient biochemical information that distinctly identifies such "chimeric molecule" other than the chimeric molecule comprising bioluminescent polypeptide and RGD motif-comprising polypeptide of SEQ ID NO:1 has not

[4] See page 4, lines 3-29, of the Office Action.

been provided. It is alleged that it would require undue experimentation for the skilled artisan to make and use any chimeric molecule comprising an RGD motif-comprising polypeptide for *in vivo* imaging of tumor neovasculature.

The Patent Office cites *In re Wand* as providing factors to be considered in determining whether undue experimentation is required to practice the invention. Guidance as to how much experimentation may be needed and still not be "undue" has been set forth by the Federal Circuit in, *e.g.*, Hybritech, Inc. v. Monoclonal Antibodies, Inc. In that case, an applicant had claims that were generic to all IgM antibodies directed to a specific antigen. However, only a single antibody producing cell line had been deposited. The PTO rejected claims that were generic to all antibodies directed to the antigen as lacking an enabling disclosure.

The Federal Circuit reversed, noting that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody species was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

The specification on, inter alia, page 15, lines 10-25, pages 22 to 25, and Example 1, provides sufficient guidance for the skilled artisan to make and use a chimeric molecule comprising a RGD motif to detect RGD-binding polypeptides *in vivo* by computer assisted tomography (CAT) image, magnetic resonance spectroscopy (MRS) image, magnetic resonance imaging (MRI) image, positron emission tomography (PET) image, a single-photon emission computed tomography (SPECT) image or bioluminescence image (BLI) without undue experimentation. Designing RGD-motif-comprising polypeptides capable of binding RGD-binding polypeptides *in vivo* was well known in the art at the time of the invention. Analogous to Hybritech, while a certain amount of screening of RGD-motif-comprising polypeptides capable of binding RGD-binding polypeptides *in vivo* may have been necessary, the design and

screening of these compositions would only have required routine screening, not undue experimentation.

At the time of the invention, it was well known in the art that the tripeptidic sequence Arg-Gly-Asp, or "RGD," is often the primary site of recognition by integrins that are expressed on tumor cells. At the time of the invention, it was well known in the art that tumor cell-expressing polypeptides that recognize RGD-comprising polypeptides mediate tumor cell adhesion to the components of extracellular matrix and basement membrane. The specification incorporates by reference, inter alia, Fujii (1995) Biol. Pharm. Bull. 18:1681-1688; Saiki (1990) Jpn. J. Cancer Res. 81:1003-1011, which discuss the design and routine screening of RGD-motif comprising polypeptides for *in vivo* activity. The specification incorporates by reference Pasqualini (1997) Nat. Biotechnol. 15:542-546, discussing that alpha v integrins present in tumor blood vessels can bind circulating RGD-expressing peptide ligands selective for these integrins. Because making, screening and using RGD-comprising polypeptides was well known in the art at the time of the invention, only routine screening would have been needed for the skilled artisan to make and use the chimeric compounds of the invention to practice the methods of the invention. An exemplary method for testing a compound to determine if it has the desired function and is within the scope of the invention is provided, inter alia, in Example 1, page 26, of the specification.

Applicants respectfully submit that the specification enabled the skilled artisan at the time of the invention to make and use the claimed invention. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. §112, first paragraph, can be properly withdrawn.

*Written Description*

Claims 51-59 and 61-69 were rejected under 35 U.S.C. 112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Patent Office alleged that Applicants have disclosed only a chimeric molecule comprising bioluminescent polypeptide and RGD motif-comprising polypeptide of

SEQ ID NO:1; therefore, the skilled artisan cannot envision all the contemplated chimeric molecule possibilities recited in the instant claims. It further alleged that conception cannot be achieved until representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method.[5]

Applicants respectfully submit that the claimed invention is adequately disclosed in the instant application. The first domain of the chimeric molecule can be a fluorescent, bioluminescent, or chemiluminescent polypeptide or a heterologous kinase, all of which were well known in the art at the time of the invention. Furthermore, the specification sets forth several exemplary species, including aequorin, obelin, mnemiopsin, berovin, or herpes simplex virus-1 thymidine kinase.

The second domain of the chimeric molecule can be an RGD motif-comprising polypeptide, a selectin-binding polypeptide, a matrix metalloproteinase-binding polypeptide or a chondroitin sulfate proteoglycan-binding polypeptide, all of which were well known in the art at the time of the invention. Furthermore, the specification sets forth several exemplary species, including those set forth in SEQ ID NOS:1-4. The specification also provides exemplary properties of the claimed chimeric molecule on, inter alia, page 15, line 10, to page 18, line 22.

In summary, an applicant need not include disclosure that was well known in the art to satisfy the written description requirements of section 112, first paragraph. Fluorescent, bioluminescent and chemiluminescent polypeptides, heterologous kinases, RGD motif-comprising polypeptides, selectin-binding polypeptides, matrix metalloproteinase-binding polypeptides and chondroitin sulfate proteoglycan-binding polypeptides were all well known in the art at the time of the invention. Additionally, the specification provides examples of each element of the claims and an exemplary chimeric molecule. Thus, the specification provides a sufficiently clear description of the claimed invention to convey to the skilled artisan that Applicants had possession of the claimed invention at the time the instant application was filed.

Accordingly, in light of the remarks set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 51-59 and 61-69 based upon 35 U.S.C. §112, first paragraph.

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[5] See page 5, lines 31-36, of the Office Action.

Issues under 35 U.S.C. §103

Claims 51-59 and 61-69 are rejected under 35 U.S.C. §103(a) a allegedly obvious over U.S. Patent No. 5,650,135 (the '135 patent), in view of U.S. Patent No. 6,087,476 (the '476 patent), and further in view of U.S. Patent No. 6,180,084 (the '084 patent).

For a proper rejection under 35 U.S.C. §103(a), the references, either alone or in proper combination, must teach or suggest all the claim limitations of Applicants' claimed invention. Applicants will show that the deficiencies of the '135 patent are not cured by the '476 and '084 patents. Accordingly, a *prima facie* case of obviousness has not been established and the rejection can be properly withdrawn.

The '135 patent discusses methods and compositions for detecting and localizing light originating from a mammal as well as methods for targeting light emission to selected regions and tracking entities within the mammal. The '135 patent discusses use of light-emitting conjugates containing a biocompatible entity and a light-generating moiety. The '135 patent discusses biocompatible entities including small molecules such as cyclic organic molecules; macromolecules such as proteins; microorganisms such as viruses, bacteria, yeast and fungi; eukaryotic cells; all types of pathogens and pathogenic substances; and particles such as beads and liposomes. The '135 patent discusses light emitting entities directed to tumor cells by liposomes containing antibodies to tumor antigens or by transforming tumor cells with a light emitting construct.

However, the '135 patent is defective, inter alia, because it does not discuss or suggest making or using a chimeric polypeptide comprising a fluorescent, bioluminescent, or chemiluminescent polypeptide or heterologous kinase in one domain and an RGD motif-comprising polypeptide, a selectin-binding polypeptide, a matrix metalloproteinase (MMP)-binding polypeptide or a chondroitin sulfate proteoglycan-binding polypeptide in a second domain.

The '476 patent discusses a luminescent chimeric protein which includes a photoprotein and a second protein which may be light- or heavy-chain immunoglobulin, an antigenic peptide, avidin, streptavidin, or protein A. The '476 patent also does not discuss or suggest making or using a chimeric polypeptide comprising a fluorescent, bioluminescent, or chemiluminescent polypeptide or heterologous kinase in one domain and an RGD motif-

comprising polypeptide, a selectin-binding polypeptide, a matrix metalloproteinase (MMP)-binding polypeptide or a chondroitin sulfate proteoglycan-binding polypeptide in a second domain. Accordingly, the '476 patent does not cure the defects in the '135 patent.

The '084 patent discusses a method for identifying a tumor homing molecule that homes to angiogenic vasculature. The '084 patent does not discuss or suggest utilizing a light emitting moiety in conjunction with any tumor homing molecule. There is no teaching or suggestion for making or using a chimeric polypeptide comprising a fluorescent, bioluminescent, or chemiluminescent polypeptide or heterologous kinase in one domain and an RGD motif-comprising polypeptide, a selectin-binding polypeptide, a matrix metalloproteinase (MMP)-binding polypeptide or a chondroitin sulfate proteoglycan-binding polypeptide in a second domain. Accordingly, the '084 patent does not cure the defects in the '135 patent.

In order to be able to combine and modify the teachings of the references, there must be some suggestion in the prior art for doing so.

> There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).
> MPEP 2143.01.

Applicants submit that prior to the filing of the present application there was no motivation for combining the references to arrive at the claimed methods. The '135 patent discusses various non-invasive imaging compositions. However, these compositions are not those used in the claimed methods, e.g., a chimeric polypeptide having a fluorescent, bioluminescent, or chemiluminescent polypeptide or heterologous kinase and a RGD motif-comprising polypeptide. The '135 patent does not discuss or suggest a chimeric polypeptide of the invention, including a chimeric polypeptide comprising a first domain having a fluorescent, bioluminescent, or chemiluminescent polypeptide or heterologous kinase and a second domain comprising an RGD motif-comprising polypeptide.

The '476 patent discusses immunoglobulins, antigenic peptides, avidin, streptavidin, or protein A. While the '084 patent discusses tumor homing molecules, there is no suggestion or motivation in this patent to combine tumor homing molecules with a light emitting polypeptide to create a construct that can be imaged.

Applicants respectfully aver that there is no teaching or suggestion in any of the cited references to make or use chimeric polypeptides used in the methods of the invention, including a fluorescent, bioluminescent, or chemiluminescent polypeptide or heterologous kinase or a RGD motif-comprising polypeptide.

Accordingly, Applicants respectfully submit that because none of the references, the '135 patent, the '476 patent nor the '084 patent alone or in combination teaches, suggests, or motivates one skilled in the art to practice Applicants' claimed methods a *prima facie* case of obviousness has not been made. In light of the remarks set forth herein, Applicants respectfully request reconsideration and withdrawal of the rejection based upon 35 U.S.C. §103 as applied to claims 51-59 and 61-69.

## CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first paragraph and 35 U.S.C. §103. Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If necessary, please apply additional and necessary charges, and apply all credits, to Deposit Account No. 06-1050.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: Nov. 14, 2002

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## Version with markings to show changes made

In the specification:

Paragraph beginning at page 26, line 20 has been amended as follows:

--The [RDG] RGD-luciferase was also injected into a nude mouse with an orthotopic mammary tumor. Luciferin was administered. The animal was imaged in an *in vivo* bioluminescent imaging system. As shown in Figure 2, the presence of the tumor was detected by the emission of luciferase-produced photons from the tumor site (see arrow).

[→]--

In the claims:

New claims 70 to 75 have been added.

In the drawings:

Originally filed Figures 1 and 2 have been substituted by the enclosed Figures 1 and 2.